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SENT TO: Richard Schwartz

DATE SENT: October 28, 1999

SUBJECT: Our Ref.: Classen=1A
USSN: 08/591,651

No. of pages (including this cover sheet): 12

SENT BY: Lisa Staley for Iver Cooper

Remarks:

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EXPEDITED PROCEDURE
EXAMINING GROUP

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GROUP 1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: CLASSEN, John B.
Serial No.: 08/591,651
Filed: February 12, 1996
For: METHOD AND COMPOSITION FOR AN EARLY VACCINE...

Art Unit: 1643
Examiner: B. BRUMBACK
Washington, D.C.
Atty.'s Docket: CLASSEN=1A
Date: October 27, 1999

THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

Transmitted herewith is an [ ] Amendment [XX] Response to Advisory Action and Renewed Request to Withdraw Finality in the above-identified application.

[XX] Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

[ ] No additional fee is required.

The fee has been calculated as shown below:

	(Col. 1)		(Col. 2)	(Col. 3)		Small Entity			Other Than a Small Entity	
	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra		Rate	Additional Fee		Rate	Additional Fee
Total		Minus		=		x 9	$		x18	$
Indep.		Minus		=		x39	$		x78	$
First Presentation of Multiple Dependent Claim						+130	$		+260	$
TOTAL ADDITIONAL CLAIMS FEE							$		Total	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col.1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time
If any extension of time for a response is required applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity
Response Filed Within
[ ] First - $ 55.00
[XX] Second - $190.00
[ ] Third - $435.00
[ ] Fourth - $680.00

Other Than Small Entity
Response Filed Within
[ ] First - $ 110.00
[ ] Second - $ 380.00
[ ] Third - $ 870.00
[ ] Fourth - $1360.00

[XX] Less fees ($55.00) already paid for 1 month extension of time on Sepetmer 7. 1999.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____. A duplicate copy of this sheet is attached.

[XX] A check in the amount of $135.00 is attached (check no. 23873).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR Section 1.16 and all patent processing fees under 37 CFR Section 1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR Section 1.18.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Art Unit: 1643
John B. CLASSEN	)	Examiner: B. BRUMBACK
Serial No.: 08/591,651	)	Washington, D.C.
Filed: February 12, 1996	)	October 27, 1999
For: METHOD AND COMPOSITION FOR AN EARLY VACCINE...	)	Docket No.: CLASSEN=1A

RESPONSE TO ADVISORY ACTION
AND RENEWED REQUEST TO WITHDRAW FINALITY

HAND CARRY TO EXAMINER
FAX COURTESY COPY TO RICHARD SCHWARTZ
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

S i r :

This response is directed to the Advisory Action mailed September 29, 1999.

REQUEST FOR INTERVIEW

Counsel hereby requests a telephonic interview, with the Examiner, her SPE, and Biotechnology Practice Specialist Richard Schwartz (who was involved in the prosecution of the parent case), to discuss this case, prior to action on this response. The Examiner is requested to compare calendars with her colleagues and phone counsel with a proposed date and time. Richard Schwartz is available only Monday to Thursday. Counsel is normally available on any of those days, but would prefer an interview time no earlier than 10 or later than 3.

RENEWED REQUEST FOR WITHDRAWAL OF FINALITY

MPEP §706.07(a) says that "second or any subsequent action on the merits shall be final, except where the examiner introduces a new ground of rejection, that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CRF 1.97(c)...."

The Examiner apparently construes a "new ground of

rejection" to mean simply the citation of a new statutory basis for rejection. Thus, she says that since the rejection made in paper 7, para. 4, lines 14-21 was a "scope" rejection under 35 USC §112, para. 1, the "scope" rejection made in paper 11, para. 4(a) was not a "new ground of rejection".

However, it is clear that the "statutory basis" for a rejection is not its "ground" because MPEP §707.07(d) declares that "the Examiner shall designate the statutory basis for any ground of rejection....". It continues that if the claim is rejected as too broad, "the reason for so holding should be given".

MPEP §707.07 states that "before final rejection is in order a clear issue should be developed between the examiner and applicant". It also declares that "the examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing and that a clear issue between applicant and examiner should be developed, if possible, before appeal".

We believe that the "ground of rejection" is the reason stated for imposing the rejection, and if the Examiner materially changes his reasoning in making a new "scope" rejection under 112/1, i.e., raises a new issue, that she is stating a new ground of rejection. Otherwise, applicant is denied a fair hearing because he had no reason to respond previously to the new issue raised by the Examiner.

This is consistent with the rules that (1) an amendment after final may be refused entry if it "raises a new issue", and (2) that after filing a continuation entering such amendment, the next action cannot be made "final".

In paper #7, the issue raised was whether the viral immunogen could "prevent a wide variety of viral conditions", i.e., immunize against a viral infection. In paper #11, the issue raised was instead whether it was proper to extrapolate from data on bacterial immunogens that early administration of a viral immunogen could reduce the incidence or severity of

diabetes. This is a new issue --a new ground of rejection-- that could have been raised against the prior claims.

The next new ground of rejection raised was in paragraph 4(b) of paper 11. Here the Examiner advanced the notion that the epidemiological data concerning immunization with BCG might be explained by a BCG component, heat shock protein, which is a "known tolerogen", and thus that a reduction in diabetes was an effect limited to BCG or at least HSP, and not extrapolatable to other immunogens.

The original rejection did not discuss applicant's epidemiological data (which was in the specification and therefore properly considered) and did not make any comment about BCG, let alone HSP.

The third new ground of rejection was in section 4(i). There, the Examiner made the very specific, and completely new argument, that one could not determine the proper time of human administration from the mouse and rat data, because the rates of maturation differ. The Examiner had previously questioned the extrapolation from mice to humans (page 5, line 22 to page 6, line 6), but without any specific reasoning explaining why an immunogen/protocol which prevents diabetes in mice would not also do so in humans. The Examiner had also questioned the calculation of the "dosage, method of administration, and frequency of administration" (page 6, lines 13-17), but because of an alleged inability to "predict therapeutic efficacy".

This new ground of rejection, in particular, illustrates the perniciousness of the Examiner's imposition of "finality" because when Applicants sought to add new claim 102, which was responsive to this unexpected new ground,[1] the claim was refused entry because it raised "new issues".

A fourth new ground of rejection was that "immunogens other

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[1] The claim called for "the first dose of an immunogen to be given before the subject's immune system arrives at a state of maturation comparable to that achieved at an age of 42 days after birth in a mouse or rat". It was based on page 29, lines 13-19 of the specification.

than BCG" was indefinite because of the indefiniteness of "immunogens" per se. The Examiner had previously urged that "other than BCG" was improper because it was a negative limitation.

Finally, the Advisory Action does not address at all section 2 of the June 14 request for withdrawal of finality.

PRIOR ART

The Examiner argues that since the immunogens remain functional absent the labelling, no functional relationship can exist between the labeling and the immunogens. Congress, in enacting the Food, Drug and Cosmetic Act (FDCA), recognized the existence of a functional relationship between a drug and its labeling. Thus, a new drug is not approved per se, rather it is approved for a particular indication (use). The new drug application includes "specimens of the labeling proposed to be used for such drug", see FDCA Sec. 505(b)1)(F). The FDA reviews the NDA and can refuse to approve if the testing was inadequate to show that "such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof" (see FDCA Sec. 505(d)(1)) or the results "show that such drug is unsafe for use" or "do not show that such drug is safe for use" under "such conditions" (see FDCA Sec. 505(d)(2)). Moreover, approval may be refused if "such labeling is false or misleading in any particular" (see FDCA Sec. 505(d)(7)).

One a new drug has been approved, that approval may be withdrawn for the same reasons that approval could have been withheld in the first place. See FDCA Sec. 505(e).

Moreover, the FDCA draws a distinction, for all drugs, between adulteration and misbranding. If a drug contains a substance which is deletenous to health, it is adulterated. See FDCA Sec. 501. However, even a drug free of deletenous substances can be sanctioned if it is misbranded. A drug is misbranded if "its labeling is false and misleading in any particular", see FDCA Sec. 502(a). More significantly, it is

misbranded "unless its labeling bears (1) adequate directions for use; and (2) such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." See FDCA Sec. 502(f). A possible loophole is closed by FDCA Sec. 502(j), which says that a drug is "misbranded" if it is "dangerous to health when used in the dosage manner, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof."

Prescription drugs dispensed by filling the prescription of a physician are exempt from Sec 505(f) and (j), cited above, but only if the drug bears a label presenting "the directions for use and cautionary statement, if any, contained in such prescription." FDCA Sec. 503(b)(2)

While a physician may prescribe a drug for an off-label use without violating the FDCA, such prescription may be considered medical malpractice, and insurers may refuse to pay for such use.

The Examiner proposes what we consider to be an overly restrictive definition of a "functional relationship", namely, that "without the printed indicia or numbers, the substrates lose their function." The Examiner urges that this was the case in Gulack and Miller.

In Gulack the substrate was a headband. It remained functional as a headband, only its educational function would have been lost if the integer sequence were omitted. In Miller, the substrate was a measuring cup or spoon. It could still be used as a cup or spoon if the indicia were omitted. Thus, it is clear that neither case presented a substrate whose function was totally dependent on the indicia.

Here, it is true that the immunogen (if protective in its own right) could be used to protect against the corresponding infectious disease. However, without the claimed directions for use, the clinician would not know how to use it to reduce the incidence or severity of a chronic immune-mediated disorder, and indeed might inadvertently increase the incidence or severity of

the disorder.

In determining the functionality of an immunogen, it is appropriate to consider its side effects, not just its specific immunogen effect. If the side effects are detrimental, its functionality is reduced. If the side effects are beneficial, its functionality is enhanced.

The fact the immunogen has a residual level of functionality, absent the indica, does not mean that there is no functional relationship between the immunogen and the indicia (labeling). If the latter increases the functionality of the immunogen, the necessary relationship exists and it is proper to give patentable weight to the labeling limitation.

The Examiner's interpretation of "functional relationship" as meaning necessary for the functioning of the substrate is inconsistent with the alternative holding of the Federal Circuit in In re Lowry, 32 USPQ 2d 1031 (Fed. Cir. 1994). Lowry claimed memory for storing data which comprised a particular data structure (a pyramidal and hierarchial arrangement of "attribute data objects", ADOs), a data processing system comprising a database, a CPU, and memory means for holding the claimed data structure and methods of manipulating ADOs. The Examiner rejected the memory claim under § 101, the system claims as obvious, and the method claims as anticipated. The Board reversed the § 101 rejection, and upheld the prior art rejections. According to the Board, Lowry's data structures were analogous to "printed matter" and lacked a "functional relationship" to the substrate (the memory).

On appeal, the Federal Circuit held that because Lowry's data structures upon storage in memory, cause electromagnetic changes, there is a physical change, albeit invisible to the eye, and hence the data structures are not analogous to "printed matter".

However, it continued that even assuming that the analogy is valid, the Board erred in its reliance on Gulack. It pointed out that the ADOs enabled "more efficient data processing

operations on stored data" in particular, that they "facilitate addition, deletion and modification of information stored in memory". The memory, of course, has a "function" even without Lowry's data structure. Lowry's merely structures "provided increased efficiency". However, that qualified as a "functional relationship": "In sum, the ADOs perform a function. Gulack requires no more".

We also think it worth reiterating that if the labeling is given patentable weight (as we think proper as a matter of law), it is clear that the claims are not anticipated or rendered obvious by the reference. While it is certainly normal for an immunogen to be labeled with directions for use, to immunize against an infectious disease, and with warnings of side effects like acute toxicity, applicant was the first to teach that it should be labeled to direct its early and frequent administration so as to reduce the incidence and severity of a chronic immune mediated disorder (e.g. diabetes) or to warn that late administration could increase the risk of diabetes, etc.

The PTO has effectively conceded this point, both by allowing method claims in Classen, USP 5,728,385, and by holding the present method claims to be free of the prior art.

DEFINITENESS

The Examiner continues to vacillate between the position that "immunogen other than BCG" is indefinite because the "other than BCG" is a negative limitation (see also section 3 at page 4), and the position that "immunogen" is itself "so broad as to be indefinite."

Neither position is proper. It is well settled that negative limitations are not indefinite, see MPEP § 2173.05(i), and that claims are not indefinite because they are broad, see MPEP § 2173.04.

Moreover, the second position (which we think the Examiner advanced in the May 4, 1999, Final Office Action, page 8, item "d", but not in the October 2, 1998, nonfinal Action page 7,

lines 20-21) is a new ground of rejection that could have been earlier advanced, and hence finality should have been withdrawn.

DESCRIPTION

The issue is whether Applicant may rely on the language of original PCT claims 1, 7, 12 and 13.

It is well established that the original claims of a U.S. application are a part of the original description. See MPEP § 2163.03(I), citing In re Koller, 204 USPQ 702 (CCPA 1980).

The question is whether, when a PCT application is filed which designates the U.S., and the PCT claims are amending during IPE, whether the "original" claims for purpose of 35 USC § 112 include the PCT claims as filed.

We have two independent bases for urging that they are, at least in this case.

First, 35 USC § 363 clearly states "an international application designating the United States shall have the effect, from its international filing date under article 11 of the treaty, of a national application for patent regularly filed in the Patent and Trademark Office except as otherwise provided in section 102(e) of this title." Clearly § 102(e) has nothing to do with the "description" requirement, which is based on § 112. So the international application as filed, with claims 1, 7, 12 and 13, has the same effect as a U.S. application filed that day.

Secondly, the Examiner's attention is respectfully directed to section 16 of the transmittal letter, item 4

> "A courtesy copy of the International Preliminary Examination Report with annexes. Note: Please use the claims as they appear in the IPER annexes as the claims in this case. Claims indicated as "deleted" in the annex should be deemed presented on filing but cancelled herewith by preliminary amendment, to avoid renumbering."

Hence, the PTO was instructed to treat original PCT claims

1, 7, 12 and 13 as if they had been presented at the time of national stage entry, and then, a moment later, cancelled. The original claims of a U.S. application are part of the description even if they are subsequently cancelled.

ENABLEMENT

We need to remind the Examiner that the specification is presumptively enabling (In re Marzocchi), and that evidence of enablement (animal data, or human epidemiological data) must be rebutted by more relevant evidence of non-enablement in order to overcome that presumption. See MPEP § 2164.04, 2154.05, 2164.07.

The claims are written so that inoperative embodiments are automatically excluded (note the "acting" limitation), and see MPEP § 2164.08 (b). Applicant's discovery is of the general advantage of early immunization. It is not Applicant's job to identify every possible vaccine in order to enjoy generic protection of his discovery. If another scientist later identifies a protective immunogen for HSV, HCV, HIV or CMV, and administers it before 42 days after birth to reduce the incidence or severity of diabetes, then that later scientist is profiting from Dr. Classen's discovery, and should pay tribute to it.

With regard to the effect of administering viral proteins, all viral proteins can elicit an immune response. Some elicit a protective response, others do not. Whether the response is protective or not depends inter alia, on (1) are there several strains of the virus and, if so, is the protein in question strain-specific, and (2) does the virus travel through the blood or by cell-to-cell direct contact.

With regard to HIV, CMV, and HSV in particular, immunogens are known for each. See Gringeri, et al., J. Hum. Virol. 1:293-8 (1998) (HIV-1 Tat protein); Lambert, et al., J. Acquir. Imm. Defic. Syndr. Hum. Retroviral., 1a:451-61 (1998) (HIV gp120, gp160); Limsuwan, et al., Vaccine, 16:142-9 (1998) (gp120 depleted inactivated vines HZ321); Straus, et al., J. Infect. Dis., 176:1129-34 (1997) (HSV type 2 gpD and gbB); Adler, et al.,

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Pediatr. Infect. Dis. J., 17:200-6 (1998) (live attenuated CMV Townestrain), copies of abstracts enclosed.

On the issue of maturation, mice develop faster than humans. If we give a dose of vaccine before 42 days of age in mice, and it reduces the incidence or severity of diabetes, then giving the same vaccine at the same time to humans should also be effective, because, at the same age, the human will be at an even earlier stage of maturation than the mouse. In our examples, the day of first administration was day 8 in Example 1, day 1 in Example 2, day 10 in Example 3, day 1 in Example 4 (rate), and day 1 in Example 5. Even day 8 in the mouse will certainly correspond to a very young human.

The Examiner did not seem to understand the issue of the virus infection (page 10). Viruses replicates at the same rat in mice and humans. Early immunization causes interferon release which slows the replication of viruses which increase the risk of diabetes.

Respectfully submitted,

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